Vitamin C induces Tet-dependent DNA demethylation and a blastocyst-like state in ES cells.

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Public Summary:
DNA methylation is a heritable epigenetic modification involved in gene silencing, imprinting, and the suppression of retrotransposons. Global DNA demethylation occurs in the early embryo and the germ line, and may be mediated by Tet (ten eleven translocation) enzymes, which convert 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC). Tet enzymes have been studied extensively in mouse embryonic stem (ES) cells, which are generally cultured in the absence of vitamin C, a potential cofactor for Fe(II) 2-oxoglutarate dioxygenase enzymes such as Tet enzymes. Here we report that addition of vitamin C to mouse ES cells promotes Tet activity, leading to a rapid and global increase in 5hmC. This is followed by DNA demethylation of many gene promoters and upregulation of demethylated germline genes. Tet1 binding is enriched near the transcription start site of genes affected by vitamin C treatment. Importantly, vitamin C, but not other antioxidants, enhances the activity of recombinant Tet1 in a biochemical assay, and the vitamin-C-induced changes in 5hmC and 5mC are entirely suppressed in Tet1 and Tet2 double knockout ES cells. Vitamin C has a stronger effect on regions that gain methylation in cultured ES cells compared to blastocysts, and in vivo are methylated only after implantation. In contrast, imprinted regions and intracisternal A particle retroelements, which are resistant to demethylation in the early embryo, are resistant to vitamin-C-induced DNA demethylation. Collectively, the results of this study establish vitamin C as a direct regulator of Tet activity and DNA methylation fidelity in ES cells.

Scientific Abstract:
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